THE AETIOLOGY OF RENAL STONE: A NEW CONCEPT ARISING FROM STUDIES ON A STONE-FREE POPULATION

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JOHN HUNTER WAS interested in renal stone formation and his views, expressed almost 200 years ago, are still in accord with current concepts. He recognized that there existed a similarity between stone formation and calcification, for in describing the formation of the enamel of the teeth he wrote: " The operation is similar to the formation of the shell of the egg, the stone in the kidneys and bladder, and the gall stone ". He appreciated too that stone formation occurs by a process of crystallization, for he also wrote: " The author has made many experiments on the formation of different calculi and finds that they are formed by crystallisation " (Hunter, 1771).

Renal stone appears to have been recognized throughout medical history and is among the oldest documented medical disorders of mankind. Shattock (1905) described a stone which was found in an Egyptian grave dating from the Second Dynasty. The date of this tomb was about 4400 B.C. The calculus was very irregular in shape, approximately 1.5 cm. at its longest diameter and was composed of calcium carbonate and phosphate, with a small amount of calcium oxalate. Down to the Renaissance, stone in the kidney, or at least renal colic, was not infrequently mentioned in medical writings, but up to the end of the 18th century chemical science was as yet too inadequate to enable any rational conjecture as to the composition of urinary calculi to be made. Paracelsus (1490–1541), for example, held that poison from food became deposited upon the teeth, or in the organs, in the form of what he called " tartar ", and he regarded this deposit as the cause of gout and stone.

Speculation as to the composition and cause of renal stone dates from the chemistry of urine at the end of the 18th century. Urea was discovered by Rouelle le Cadet in 1773 and uric acid isolated from the urine by Scheele in 1776, who made the first chemical observation on the subject of calculi. It was found in urinary concretions by Wollaston in 1797, who in 1810 also discovered cystine in certain calculi. The phosphates had previously been discovered by the alchemists on distilling urine with lime. These discoveries had certain effects. They stimulated the idea that calculi could be dissolved by injecting suitable solvents into the bladder and they aroused interest in the possible influence of diet on stone formation. For the most part writings of the latter part of the 18th century and the

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early part of the 19th century dealt with the chemical composition of urinary calculi and views on their causation in terms of composition. Monographs and papers dealing with the subject appeared sporadically and fascinating contributions were made by several authors. In 1779 Dodson in his *Commentary on Fixed Air* reported on a statistical inquiry which he conducted into the frequency of stone in various parts of England and concluded that hard water prevents the formation of stone. In 1792 Wilson wrote *On the causes of urinary gravel* and Wollaston in 1796 described the nature of no less than four species of human concretions—gouty concretions, fusible calculus, mulberry calculus and calculus from the prostate—and in 1810 he discovered " cystic oxyd ". Foucroy (1801) published several papers on the subject of stone and his *Systême des Connoissances Cliniques* contained an elaborate sketch of urinary calculi. In 1817 Alexander Marcet wrote *An essay on the chemical history and medical treatment of calculus disorders* and on the basis of colour and appearance listed 13 types of stone, gave their chemical composition, and commented on " the remarkable simplicity which modern chemistry has introduced in the history of calculi ". John Howship in 1823 wrote *A practical treatise on the symptoms, causes, discrimination and treatment of some of the most important complaints that affect the secretion and excretion of the urine* and described various " stone diatheses ", viz. phosphate diathesis, lithic acid diathesis and oxalate of lime diathesis, and with regard to their causation stated that most writers agree that they very often originate in some strain or other injury of the back. For the remainder of the 19th century very little attention appears to have been paid to the problem.

There is a great deal in the medical literature of the 20th century dealing with factors supposedly concerned in the initiation and development of renal calculi, but a critical appraisal of the considerable amount of published data reveals that efforts directed towards an understanding of their causation have met with extraordinarily little success. It is not the purpose of this lecture, however, to discuss the numerous theories on renal stone formation that have been put forward but to present a new concept concerning aetiology.

Most of the published data concerning the aetiology of renal stone have been obtained either by means of experimental studies in the laboratory or by means of comparative studies of normal individuals and patients who have formed a renal stone. The criticism that can be levelled at experimental studies is that conditions *in vitro* do not necessarily parallel conditions *in vivo*. Data obtained by means of comparative studies of normal individuals and renal stone patients could also be of questionable value for the following reason. The recurrence rate of renal stone has variously been reported as ranging from 9 per cent (Twinem, 1937; Baker and Connelly, 1956; Modlin, 1957) to 15 per cent (Prince and Scardino, 1960). Williams (1963) reported an exceedingly high recurrence rate of 75 per cent, but he appears to have studied a highly selected group of patients. An accurate assessment of the recurrence rate of renal stone is extremely difficult, but whatever the true figure may be it is abundantly clear that renal stone formation occurs as a series of intermittent episodes rather than as a continuous uninterrupted process. One may therefore be seeking the nature of the temporary or transient disturbance that resulted in stone formation long after it has ceased to operate, the stone being the only remaining evidence of the episode. A comparative study of a stone-prone group and a stone-free group of individuals within one population would obviously provide data of far greater significance.

The population of the Republic of South Africa is somewhat heterogeneous, but is basically made up of two main groups, the white population and the indigenous group, the Bantu. The non-infective diseases of the Bantu display certain important differences from those encountered among the white population. For example, whereas endomyocardial fibrosis, idiopathic cardiomyopathy, siderosis, porphyria, primary carcinoma of the liver, kwashiorkor and haemaglobinopathies commonly occur in the Bantu, coronary thrombosis, pulmonary embolism, thyrotoxicosis, disseminated sclerosis, gallstones and rheumatoid arthritis are rarely encountered. The occurrence of renal stone in the Bantu is also extremely rare (Vermooten, 1941; Lopis and Kaplan, 1948; Muskat, 1951; Politzer and Beuchat, 1957; Wise and Kark, 1961), and I have personally never attended a Bantu patient with a renal stone. Renal stone occurs in the white population, however, with no less frequency than in other Western communities. This situation is somewhat unique and provides near-ideal conditions for a study of the aetiology of renal stone.

It is accepted that the anatomy and physiology of the Bantu are in no way different from that of the white group. It is also known that the American negro, who springs from the same stock as the Bantu, form renal stones as commonly as the rest of the American population (Dodson and Clark, 1946). Why then in the Bantu do the urinary salts not crystallize to form renal stones? It seems reasonable to assume that the answer to the problem may be found in differences between the composition of urine in white and Bantu persons. In pursuance of this premise, 24-hour collections of urine obtained from normal white and Bantu males were analysed for volume, pH, osmolality, magnesium, potassium, total calcium, ionized calcium, sodium, ammonia, sulphate, phosphate and citric acid. The results are shown in Table I. The choice of male subjects for this study was suggested by the known higher incidence of renal stone in this sex. The mean 24-hour urinary excretion of magnesium, potassium, ammonia and sulphate did not differ significantly in the white and Bantu groups. The mean 24-hour urinary volume, osmolality, ionized calcium and sodium were higher in the Bantu than in the white subjects. The mean 24-hour urinary pH, total calcium, phosphate and citric acid were lower in the Bantu than in the white subjects. All the

TABLE I

TWENTY-FOUR-HOUR URINARY CONSTITUENTS IN NORMAL WHITE AND BANTU SUBJECTS

Description	*No.*	*White* *Range*	*Mean*	*S.D.*	*No.*	*Bantu* *Range*	*Mean*	*S.D.*	*Significance of Difference*
Magnesium (mg.) ..	103	23–277	122	40	128	4–274	113	63	P<0.2
Potassium (mEq.) ..	87	34.6–171.8	87.6	31.0	96	22.6–181.6	81.8	33.6	P<0.3
Ammonia (mEq.) ..	88	24.7–83.4	47.5	15.4	94	15.6–90.3	48.7	24.5	P<0.7
Inorganic sulphate (mEq.)	91	17.0–66.6	36.3	12.3	50	13.7–73.1	34.6	11.5	P<0.5
Volume (ml.)	103	560–2540	1248	483	128	660–4044	1875	706	P<0.001
Osmolality (mOsm.) ..	60	360–1236	830	210	60	256–917	1100	332	P<0.001
Ionized calcium (mg.)	64	2.4–80.5	26.1	15.7	66	8.5–150	35.0	27.8	P<0.05
Sodium (mEq.) ..	103	79–496	213	79	128	123–632	292	106	P<0.001
pH	103	5.3–7.0	6.2	0.49	128	5.1–7.3	6.0	0.57	P<0.005
Calcium (mg.) ..	103	15–537	138	74	128	8–352	81	56	P<0.001
Inorganic phosphate (mg.)	103	383–1470	940	236	128	73–1800	614	314	P<0.001
Citric acid (mg.) ..	103	170–1405	517	207	128	40–1667	353	235	P<0.001

differences were highly significant (Fig. 1). Most of these differences in urinary composition probably reflect differences in dietary habits (Modlin *et al.*, 1963). The low urinary output of calcium in the Bantu is probably more complicated than a simple relationship to dietary intake and was found to be the same in urban and rural Bantu although the calcium intake is markedly different in these two Bantu groups (Walker, 1954).

The significance of these findings in relation to the aetiology of renal stone was considered.

The urinary constituents that have in the main been studied by various investigators in relation to renal stone formation are magnesium, phosphate, citric acid, ionized calcium and total calcium. Conflicting conclusions have been arrived at in respect of each of these. The difference

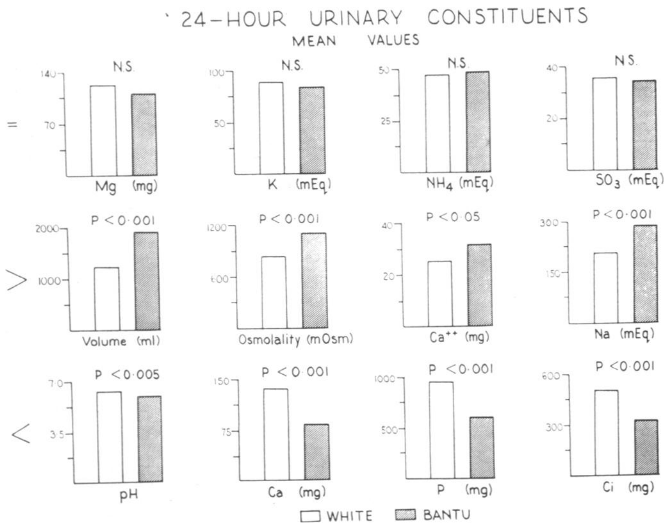


Fig. 1. Twenty-four-hour urinary constituents in normal white and Bantu subjects. Mean values. = no significant difference between white and Bantu; > Bantu significantly higher than white; < Bantu significantly lower than white.

that existed in the urinary content of each of these substances between the white and Bantu group has accordingly been evaluated for any significance in relation to renal stone formation. For the purpose of further comparison a group of patients who had formed a renal stone was studied as well. The results obtained in this study are discussed in the first part of this lecture.

Magnesium (Table II)

Previous data suggest that urinary levels of magnesium may play a part in the genesis of renal stone. Hammarsten (1936) found that the solubility of calcium is increased in the presence of magnesium, and Howard (1962) showed that magnesium is a decided deterrent to *in vitro* calcification. Magnesium deficiency has been reported as being responsible for nephrocalcinosis (Cramer, 1932), and Faragalla and Gershoff (1961) demonstrated that diets high in magnesium protected Vitamin B_6-deficient rats against stone formation.

TABLE II

TWENTY-FOUR-HOUR URINARY MAGNESIUM IN NORMAL WHITE AND BANTU SUBJECTS AND PATIENTS WITH RENAL STONE

		Magnesium mg. per 24 hr.		
Description	*Number*	*Range*	*Mean*	*S.D.*
1. White subjects ..	103	23–277	122	40
2. Bantu subjects ..	128	4–274	113	63
3. Stone cases ..	60	32–220	105	39

Significance of differences: 1 : 2 $P < 0.2$; 1 : 3 $P < 0.01$; 2 : 3 $P < 0.3$

In this study the mean 24-hour urinary magnesium in the Bantu did not differ significantly from that in the white group. Although the white group had a significantly higher mean 24-hour urinary excretion of magnesium than the stone cases ($P < 0.01$), there was no significant difference in mean daily urinary magnesium between the Bantu and stone cases (Fig. 2).

These findings suggest that there is no apparent relationship between daily levels of urinary magnesium *per se* and the tendency to renal stone formation.

Inorganic phosphate (Table III)

The mean 24-hour urinary phosphate was significantly higher in the white group than in the Bantu ($P < 0.001$). This created an initial impression that high urinary phosphate levels might be a factor in renal stone formation. Further inspection of the data reveals, however, that the mean 24-hour urinary phosphate was significantly lower in the stone cases than in the normal white subjects ($P < 0.001$), which is contrary to what is expected if high levels of urinary phosphate were contributory to renal stone formation (Fig. 2).

Citric Acid (Table IV)

The suggestion that low levels of urinary citric acid may play a part in the formation of calcium-containing renal stones has been made by numerous investigators (Ostberg, 1931; Boothby and Adams, 1932; Kissin and Locks, 1941; Scott *et al.*, 1943; Nordin, 1963), and Dedmon and Wrong (1962) concluded that a reduced excretion of citrate is a causal factor in the nephrocalcinosis of renal tubular acidosis. Hodgkinson (1962) concluded, however, that the occurrence of hypocitricuria in renal stone formers did not appear to be frequent or marked, and Canary *et al.* (1964) reported that their data suggested that renal stone formation was not due to any absolute decrease in urinary citrate excretion.

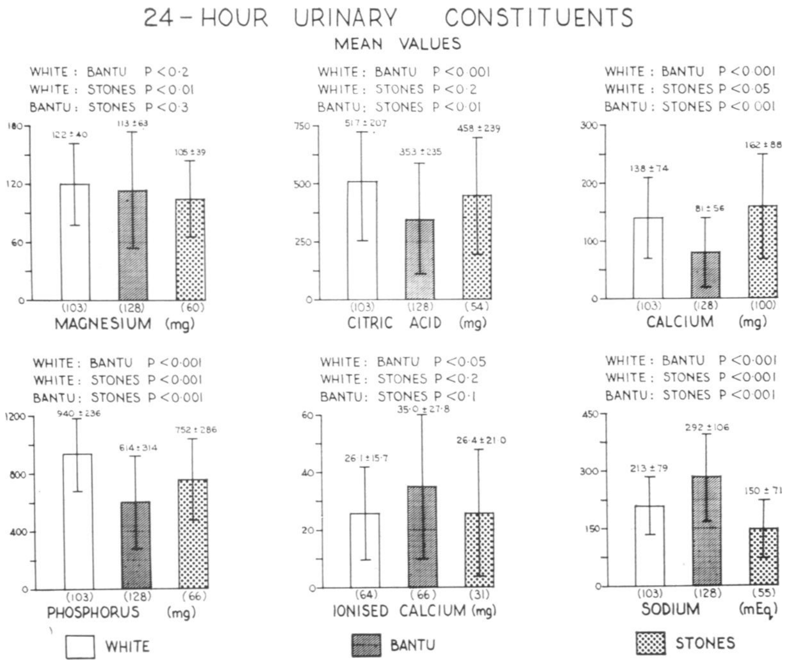


Fig. 2. Twenty-four-hour urinary constituents in normal white and Bantu subjects and patients with renal stone. Mean values. The number of subjects in each group is shown in brackets.

The results obtained in the present study showed that the mean 24-hour urinary citric acid was significantly lower in the Bantu than in the white group ($P < 0.001$) and also significantly lower in the Bantu than in the stone cases ($P < 0.01$). The mean 24-hour urinary citric acid in the white group did not differ significantly from that in the stone cases (Fig. 2).

These findings indicate that there is no apparent relationship between low urinary levels of citric acid and the liability to renal stone formation.

TABLE III

TWENTY-FOUR-HOUR URINARY INORGANIC PHOSPHATE IN NORMAL WHITE AND BANTU SUBJECTS AND PATIENTS WITH RENAL STONE

		Inorganic phosphate mg. P per 24 hr.		
Description	*Number*	*Range*	*Mean*	*S.D.*
1. White subjects ..	103	383–1470	940	236
2. Bantu subjects ..	128	73–1800	614	314
3. Stone cases ..	66	124–1354	752	286

Significance of differences: 1 : 2 $P < 0.001$
1 : 3 $P < 0.001$
2 : 3 $P < 0.001$

TABLE IV

TWENTY-FOUR-HOUR URINARY CITRIC ACID IN NORMAL WHITE AND BANTU SUBJECTS AND PATIENTS WITH RENAL STONE

		Citric acid mg. per 24 hr.		
Description	*Number*	*Range*	*Mean*	*S.D.*
1. White subjects ..	103	170–1405	517	207
2. Bantu subjects ..	128	40–1667	353	235
3. Stone cases ..	54	127–1176	458	239

Significance of differences: 1 : 2 $P < 0.001$
1 : 3 $P < 0.2$
2 : 3 $P < 0.01$

TABLE V

TWENTY-FOUR-HOUR URINARY IONIZED CALCIUM IN NORMAL WHITE AND BANTU SUBJECTS AND PATIENTS WITH RENAL STONE

		Ionized calcium mg. per 24 hr.		
Description	*Number*	*Range*	*Mean*	*S.D.*
1. White subjects ..	64	2.4–80.5	26.1	15.7
2. Bantu subjects ..	66	8.5–150	35.0	27.8
3. Stone cases ..	31	0–75	26.4	21.0

Significance of differences: 1 : 2 $P < 0.05$
1 : 3 $P < 0.2$
2 : 3 $P < 0.1$

TABLE VI

CONCENTRATION AND PROPORTION OF URINARY IONIZED CALCIUM IN NORMAL WHITE AND BANTU SUBJECTS AND PATIENTS WITH RENAL STONE

		Ionized calcium mg. per 100 ml.			Percentage of total 24 hr. calcium		
Description	*Number*	*Range*	*Mean*	*S.D.*	*Range*	*Mean*	*S.D.*
1. White subjects	64	0.4–7.2	2.4	1.3	3.6–52.2	21.1	10.9
2. Bantu subjects	66	0.4–6.8	1.8	1.3	13.8–100	44.9	23.2
3. Stone cases ..	31	0–4.3	1.6	1.2	0–33.5	12.6	7.5

Significance of differences:	mg. per 100 ml.	Percentage of total
	1 : 2 $P < 0.01$	1 : 2 $P < 0.001$
	1 : 3 $P < 0.01$	1 : 3 $P < 0.001$
	2 : 3 $P < 0.4$	2 : 3 $P < 0.001$

Ionized calcium

Vermeulen *et al.* (1956) concluded that calcium-binding presumably plays a role in increasing the solubility of calcium salts in urine, and Raaflaub (1963) reported that the ionic calcium concentration in urine is responsible for the precipitation tendency of calcium salts which do not readily go into solution. Vermeulen *et al.* (1956) could find no difference, however, in the proportion of ionized calcium when normal urine was compared with urine from stone-forming patients, and Thomas and Howard (1959) reported that their studies showed that ionized calcium was not raised in the urine of stone formers. Nordin and Trebidi (1962)

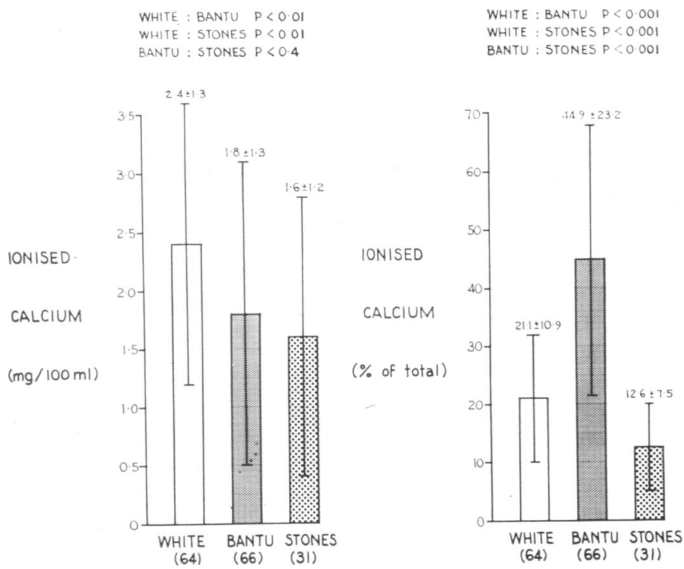


Fig. 3. Concentration and percentage of urinary ionized calcium in normal white and Bantu subjects and patients with renal stone. Mean values. The number of subjects in each group is shown in brackets.

have reported, however, that the proportion of urinary ionized calcium was higher in patients with renal stone than in normal subjects.

The results obtained in the present study are considered below.

Twenty-four-hour urinary ionized calcium (*Table V*)

The mean 24-hour urinary ionized calcium was significantly higher in the Bantu than in the white group ($P < 0.05$). There was no significant difference in the mean 24-hour urinary ionized calcium between the white group and the stone cases, or between the Bantu and the stone cases (Fig. 2).

Concentration of urinary ionized calcium (*Table VI*)

The mean urinary ionized calcium concentration was significantly higher in the white group than in the Bantu ($P < 0.01$). There was no significant difference, however, in the mean urinary ionized calcium concentration between the Bantu and stone cases (Fig. 3).

Proportion of urinary ionized calcium (Table VI)

The mean proportion of urinary ionized calcium was significantly higher in the Bantu than in the white group ($P < 0.001$), and was also significantly higher in both the Bantu and the white group than in the stone cases ($P < 0.001$) (Fig. 3).

The data presented above indicate that the daily level or concentration of urinary ionized calcium are not important factors in renal stone formation; nor does a high proportion of ionized calcium appear to be associated with a tendency to renal stone formation.

Total calcium (Table VII)

The concept of a cause and effect relationship between the degree of calciuria and renal stone formation has stimulated a considerable amount

TABLE VII

TWENTY-FOUR-HOUR URINARY CALCIUM IN NORMAL WHITE AND BANTU SUBJECTS AND PATIENTS WITH RENAL STONE

	Description	*Number*	*Calcium mg. per 24 hr.* *Range*	*Mean*	*S.D.*
1.	White subjects ..	103	15–537	138	74
2.	Bantu subjects ..	128	8–352	81	56
3.	Stone cases ..	100	30–485	162	88

Significance of differences:
1 : 2 $P < 0.001$
1 : 3 $P < 0.05$
2 : 3 $P < 0.001$

of interest since Flocks (1939) originally reported that the urinary excretion of calcium is high in many patients with renal stone. Hodgkinson and Pyrah (1958) concluded that a high urinary excretion of calcium does not by itself result in stone formation but it increases the chance that stone formation will occur. Henneman (1959) regarded the urinary excretion of calcium greater than 150 mg. per day as representing " hypercalciuria " and considered that the degree of calciuria is related to stone formation. Malm (1963) stated that there is no clear-cut data to indicate that a high urinary calcium *per se* increases the risks of renal stone formation. It is apparent, therefore, that the relationship between the two has not as yet been completely clarified and recent views are still conflicting.

The results obtained in the present study are shown in Figure 2. The mean daily urinary calcium in the white group was significantly higher than in the Bantu ($P < 0.001$). The mean daily urinary calcium in the stone cases was significantly higher than in the normal white ($P < 0.05$). At first sight these findings appear to reinforce the concept of a cause and effect relationship between the degree of calciuria and renal stone formation. Further examination of the data, however, casts considerable doubt on the validity of such a conclusion. Reference to the frequency polygon (Fig. 4) shows that renal stone formation occurred in the presence of any given level of daily urinary calcium, and that the range of daily urinary calcium values was similar in the stone patients and in the normal white subjects. It is also apparent from Figure 4 that the Bantu, who do not form renal stones, have a similar range of daily urinary calcium values as members of the other ethnic group who do form renal stones. Thus, renal stone may or may not occur with similar amounts of calcium present in the urine and the amount of daily urinary calcium *per se* cannot therefore be the critical factor in renal stone formation.

Several observers (Flocks, 1939; Hodgkinson and Pyrah, 1958; Sutherland, 1954; Cottet *et al.*, 1957; Melick and Henneman, 1958) have

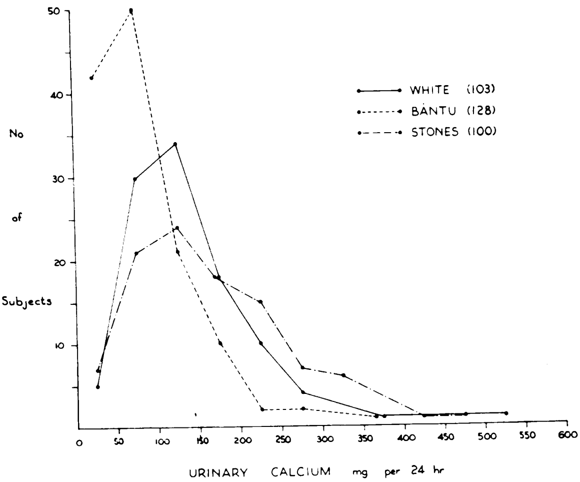


Fig. 4. Frequency distribution of 24-hour urinary calcium in normal white and Bantu subjects and patients with renal stone. The number of subjects in each group is shown in brackets.

variously reported that from 58 to 75 per cent of their patients with renal stone excreted more than 200 mg. of urinary calcium per day as compared with from 26 to 31 per cent of normal individuals. Using the same arbitrarily selected value of 200 mg. urinary calcium per day, 30 per cent of the stone patients in the present study exceeded this figure as compared with 15.5 per cent of the normal white subjects. The apparent relationship between the degree of calciuria and renal stone formation suggested by this observation was tested (Table VIII). No significant association was found ($X^2 = 0.6$, $P < 0.5$). Moreover, 90 per cent of the stone patients fell within the upper limit of normality of daily urinary calcium defined as the mean daily output of calcium by the normal individuals plus two standard deviations, which is a very close approximation to the 95 per cent of normal individuals that could be statistically expected to do so.

This evidence indicates that no clear-cut cause and effect relationship can be established between the degree of calciuria *per se* and renal stone formation.

The important conclusions that could be reached from all the foregoing observations are that factors other than the absolute daily urinary level of total calcium, ionized calcium, citric acid, phosphate and magnesium, or concentration or proportion of urinary ionized calcium, appear to be of importance in the genesis of calcium-containing renal stone. It was apparent, therefore, that a different approach to the problem was required.

Recent work on calcification has led to a new concept of the mechanism involved. Royer, in 1928, introduced the term " epitaxy " to describe the phenomenon of crystalline intergrowth or orientated overgrowth. The Greek term epitaxy, translated literally, means " on-arrangement ". Royer concluded that several conditions must be satisfied for an induced orientation, but the most important one appears to be that the two crystal

TABLE VIII

DEGREE OF CALCIURIA—SIGNIFICANCE OF DIFFERENCE BETWEEN STONE CASES AND NORMAL WHITE SUBJECTS BY X^2 TEST

	24-hour urinary calcium		
	$>$ 200 *mg.*	$<$ 200 *mg.*	
Stone cases ..	30	70	$X^2 = 0.6$
White subjects ..	16	87	$P < 0.5$

faces in contact must have a sufficiently similar crystalline lattice. Neuman and Neuman (1958) suggested that calcification is based on this principle of epitaxy, or seeding, rather than on precipitation. They suggested that a crystalline structure, which is sufficiently similar to the crystalline structure of hydroxy apatite, is able to induce the aggregation of a nucleus of calcium and phosphate ions. Given this crystal nucleus of hydroxy apatite, the body fluids are sufficiently supersaturated to form a complete crystal spontaneously. They suggested, moreover, that hydroxy apatite can in fact serve as its own host crystal in epitaxy. It is also known that crystals of one substance may seed a supersaturated solution of another substance very efficiently provided their crystalline structure is sufficiently similar.

Studies of the composition of renal stones have shown that they are crystalline in structure (Prien, 1949; Lagergren, 1955; Murphy and Pyrah, 1962) and the principles of calcification enunciated by Neuman and Neuman would appear to be equally applicable to renal stone formation. It is more than likely that several substances in urine could possess a crystalline structure sufficiently similar to that of hydroxy apatite to act as the host crystal and induce the aggregation of ions to form the initial hydroxy apatite crystal. Mucoproteins or other crystals in urine are possible examples of such substances. Crystal aggregation could then proceed by a process of epitaxy with the ultimate formation of a renal stone. As a logical extension of this hypothesis it must be postulated that this process is normally arrested by the presence in urine of crystallization inhibitors. Fleisch and Bisaz (1962) suggested that urinary inorganic pyrophosphate possesses this property of crystallization inhibition but concluded that it could not be the only such substance present in urine for, although urinary inorganic pyrophosphate levels are appreciably higher in normal men than in normal women, renal stone occurs more frequently in men. Lewis *et al.* (1966) reported that there is little difference in the excretion of pyrophosphate in normal and calculous subjects and that a reduced urine content of pyrophosphate is unlikely to be important in the development of renal calculi. The role of urinary inorganic pyrophosphate as a crystallization inhibitor is therefore uncertain.

The possible existence of some other form of crystallization inhibitor mechanism was sought in the urine of the Bantu.

Scrutiny of the data relevant to the other urinary constituents investigated in this study revealed that the urinary output of sodium by the

TABLE IX

TWENTY-FOUR-HOUR URINARY SODIUM IN NORMAL WHITE AND BANTU SUBJECTS AND PATIENTS WITH RENAL STONE

			Sodium mEq. per 24 hr.	
Description	*Number*	*Range*	*Mean*	*S.D.*
1. White subjects ..	103	79–496	213	79
2. Bantu subjects ..	128	123–632	292	106
3. Stone cases ..	55	31–382	150	71

Significance of differences:
1 : 2 $P < 0.001$
1 : 3 $P < 0.001$
2 : 3 $P < 0.001$

Bantu was strikingly high (Table IX). It was also observed that the mean 24-hour urinary sodium was significantly higher in the Bantu than in the white group ($P < 0.001$), and significantly higher in the white group than in the stone cases ($P < 0.001$) (Fig. 2). It was apparent, therefore, that the average daily output of sodium was lowest in the stone cases and highest in the Bantu who rarely form stone. The significance of this finding appeared to require further evaluation, since as early as 1929 Meyer, in explaining the conditions for solubility of urinary salts which do not readily go into solution on the basis of simple physico-chemical laws, had observed the resulting increase in their solubility by added sodium chloride. There is also experimental evidence that sodium can act as an inhibitor of calcification. Sobel and Hanok (1952) studied calcification *in vitro*, using hypertrophic epiphyseal cartilage as an indicator. X-ray diffraction studies showed that the new mineralization obtained has the same lattice for calcification *in vitro* as that found for calcification *in vivo*, namely apatite. They found that if the bone sections were first shaken for two hours with solutions containing 150 milliequivalents per litre of calcium chloride plus sodium chloride and then incubated in the calcifying solution, calcification was inactivated. If following inactivation the bone sections were washed with distilled water and then shaken for one hour with 150 milliequivalents per litre of calcium chloride solution free of sodium chloride, calcification took place when the bone sections were again incubated in the calcifying solution. They concluded that this effect of sodium chloride was due to competition between sodium and calcium ions for the target matrix.

Evidence that sodium may inhibit renal stone formation as well has been provided by animal studies. Urolithiasis has been a problem in the cattle and sheep fattening industry for many years. Udall and Fu Ho Chen Chow (1963) fed sodium chloride at a level of 10 per cent of the total dry matter of the ration to 48 of 96 lambs. After slaughter 29 of the 48 lambs without dietary salt had renal calculi, but there was no detectable stone formation among the 48 lambs receiving sodium chloride. Udall and Fu Ho Chen Chow actually attributed this effect of sodium chloride to the action of the chloride ion.

There is evidence, therefore, that sodium can increase the solubility of calcium in the urine and that it can also inhibit calcification *in vitro* and renal stone formation *in vivo*. It seemed reasonable to conclude that a similar mechanism might account for each of these three phenomena and some indication of its nature was therefore sought. The answer appears to lie in experimental work carried out by Neuman and Neuman in 1953 concerning the solubility of hydroxy apatite, which appears to have gone unnoticed in relation to the problem of renal stone formation. These investigators demonstrated that sodium can increase the apparent solubility of hydroxy apatite and that this occurs by substitution of normal crystal lattice ions. It appears from their data that in aqueous medium the calcium ion is displaced from the solid by the entering sodium ions, and apparently the sodium ion can react with the crystal even in non-aqueous medium. This competition between the two ions has also been recognized to occur in various tissues. Niedergerke and Luttgau (1957) have demonstrated competitive binding of calcium and sodium for a component of the cell membrane of cardiac muscle, and Howell *et al.* (1960) showed that sodium and calcium are both bound by connective tissue mucopolysaccharides and that an increase in the interstitial concentration of one ion may displace the other from these substances. These data appear to provide an explanation of how sodium could act both as an inhibitor of calcification and of renal stone formation.

An enquiry into the relationship between daily urinary sodium and calcium immediately suggested itself as the most logical application of these data to the problem of renal stone formation in human beings.

There is evidence that calcium and sodium transport by the kidney are interrelated. Grollman *et al.* (1962), using stop-flow techniques, concluded that the pattern of tubular reabsorption of calcium bears many similarities to that of sodium reabsorption. A similar relationship was demonstrated by Lassiter *et al.* (1963), using micropuncture techniques. Walser (1961) reported that the tubular cells tend to maintain a constant ratio of sodium to free calcium ions in the tubular fluid. There appeared to be no data, however, concerning the relationship between 24-hour urinary sodium and calcium. Observations were accordingly made on three normal adult males, in each over a varying period of time. A

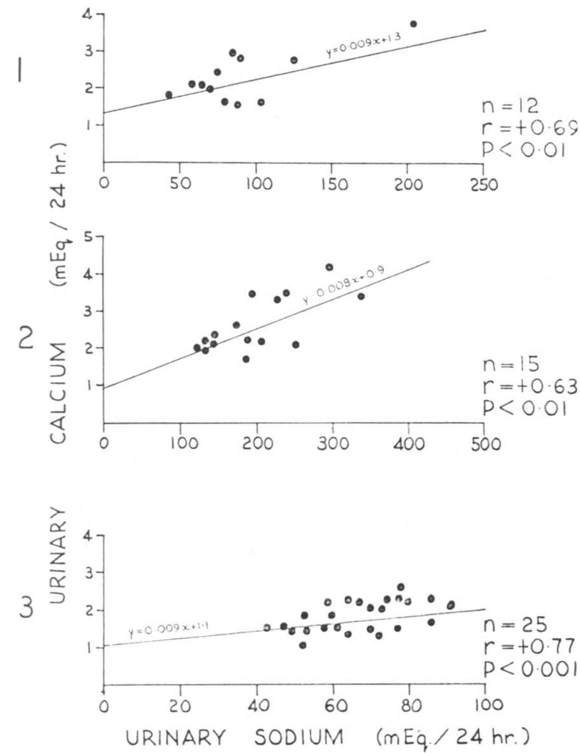


Fig. 5. Relation between 24-hour urinary sodium and calcium in three normal adult males, in each for a varying period of time. Subject 1: 12 days; Subject 2: 15 days; Subject 3: 25 days.

significant degree of correlation between 24-hour urinary calcium and sodium was demonstrated in each of the three subjects studied (Fig. 5). The relationship between the urinary excretion of sodium and calcium was accordingly studied in the normal white subjects and in the normal Bantu subjects. A significant degree of correlation between 24-hour urinary calcium and sodium was demonstrated in each of these groups (Fig. 6). Observations were next made on the stone patients. A significant degree of correlation between 24-hour urinary sodium and calcium was demonstrated in this group as well (Fig. 6). The data obtained indicated that a direct relationship existed between the daily urinary content of calcium and sodium in each of the three groups of subjects studied and renal stone formation could therefore not be related to any difference in this respect between the three groups.

Was there any other difference in the relationship between daily urinary

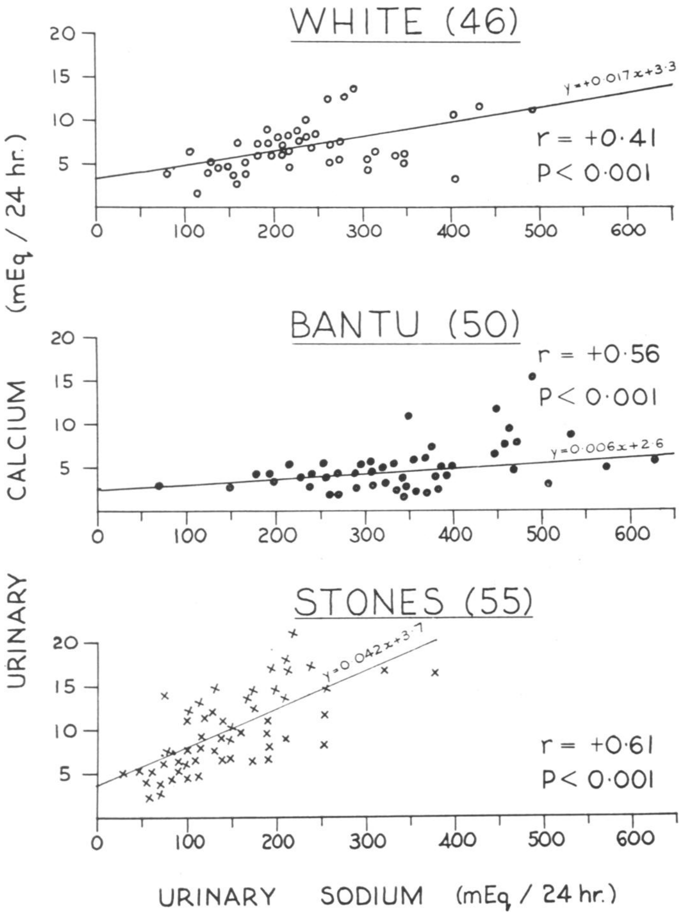


Fig. 6. Relation between 24-hour urinary sodium and calcium in normal white and Bantu subjects and patients with renal stone. The number of subjects in each group is shown in brackets.

sodium and calcium in the three groups of subjects that could be associated with renal stone formation?

Referring again to further experimental data of Neuman and Neuman (1958) relevant to the displacement of the calcium ion from the solid by the sodium ions and the resultant increase in the solubility of hydroxy apatite, which was quoted earlier, it appears that the sodium in the solid is a function of its concentration relative to calcium in solution. Prompted by this observation the amount of sodium relative to calcium was studied in the 24-hour urine of the white subjects, the Bantu subjects and the stone cases. The results are shown in Figure 7. The range of values obtained for the daily urinary sodium/calcium ratio was different in each of the three groups of subjects. The highest values of daily urinary sodium/calcium

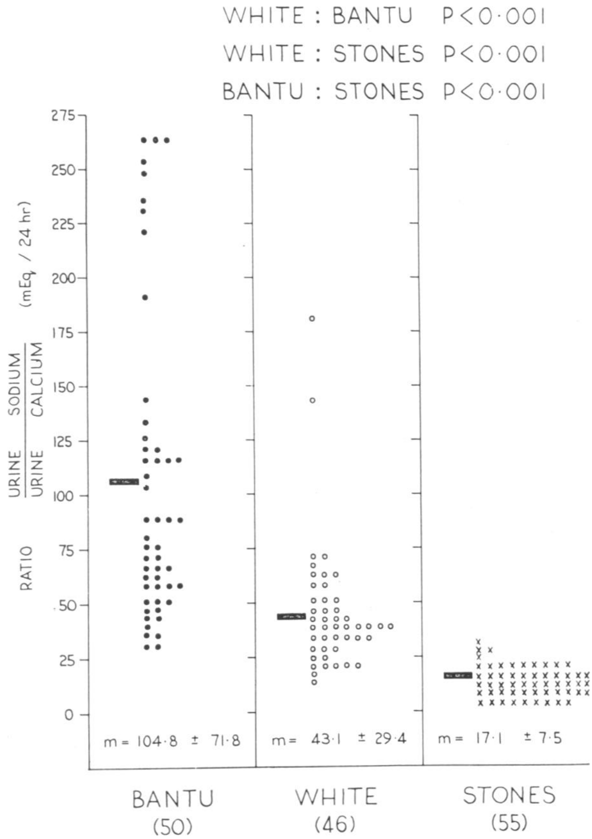
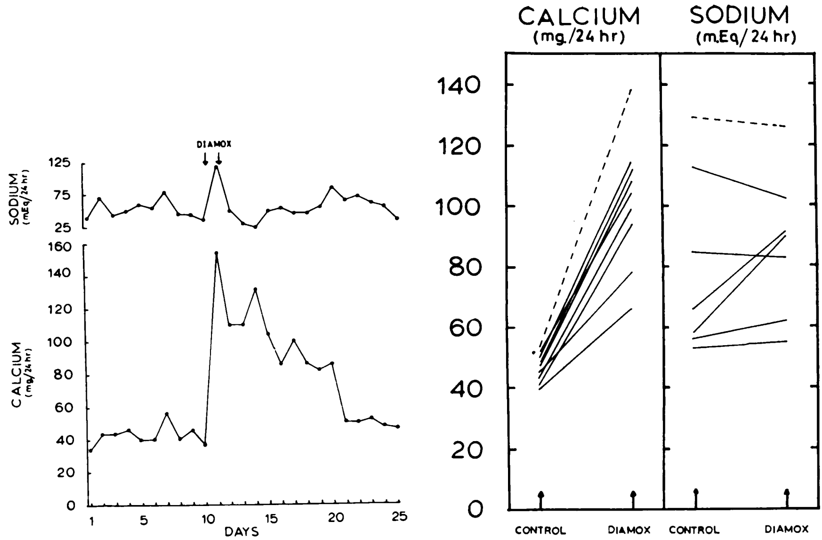


Fig. 7. Twenty-four-hour urinary sodium/calcium ratio in normal white and Bantu subjects and patients with renal stone. The horizontal bar indicates the mean value.

ratio obtained in the stone cases just attained the lowest values of daily urinary sodium/calcium ratio obtained in the Bantu, there being virtually no overlap. The highest and lowest values of daily urinary sodium/calcium ratio obtained in the white group overlapped the lowest and highest values obtained in the Bantu and stone cases respectively. It was apparent, therefore, that whereas the Bantu, who do not form renal stone, had a range of values of daily urinary sodium/calcium ratio quite different from that of the stone cases, the normal white subjects, who may or may not form renal stones, had a range of values of daily urinary sodium/calcium ratio overlapping both the range found in a group with renal stones and the range found in a group who do not form renal stones. The mean daily urinary sodium/calcium ratio was significantly higher in the Bantu than in the normal white group ($P < 0.001$), and significantly higher in the white group than in the stone cases ($P < 0.001$). There was thus an inverse relationship between the mean daily urinary sodium/calcium ratio and the liability to renal stone formation. It seemed reasonable to conclude that the tendency to renal stone formation decreases with an increasing amount of sodium relative to calcium in the urine. These findings are in accord with the experimental data.

Experimental proof of this hypothesis was sought.

Renal stone formation has been reported to occur following long-term acetazolamide therapy for glaucoma (Scheie, 1955; Becker and Middleton, 1955; Persky *et al.*, 1956; Mackenzie, 1960). This complication has been attributed to the reduction in urinary citric acid which accompanies acetazolamide administration (Gordon and Sheps, 1957; Shah *et al.*, 1958; Harrison and Harrison, 1955) but the evidence presented earlier in this study does not support this conclusion. Acute experiments were carried out to determine the effect of acetazolamide on urinary sodium and calcium. Diamox (acetazolamide) was administered orally on two consecutive days to normal adult males in an undivided daily dose of 500 mg. Daily estimations of urinary sodium and calcium were carried out during control periods and following Diamox administration. The individuals were on a self-selected diet throughout the relevant periods. This contained 800 to 1,000 mg. calcium per day. The sodium intake consisted of that contained in the food plus any additional salt taken voluntarily. Similar results were obtained on each occasion and a typical example is shown in Figure 8 (*a*). The urinary sodium rose on the first day of Diamox administration but returned to pre-administration levels 24 hours later. The urinary calcium increased markedly, in some instances almost fourfold, on the first day of Diamox administration and returned to pre-administration levels over an average period of seven days, i.e. the days of Diamox administration plus the five subsequent days. This period coincides with the known duration of action of acetazolamide in the body (Hanley and Platts, 1956). The mean seven-day values of daily urinary sodium and calcium estimations during control periods and following Diamox administration in several experiments are shown in Figure 8 (*b*). The mean urinary calcium rose significantly in every instance, whereas the mean urinary sodium either rose or fell slightly, but not significantly. These alterations in the daily urinary levels of sodium and calcium were associated with a disturbance in the correlation between the two ions, the correlation coefficient being reduced to a non-significant level in each instance (Fig. 9).



(*a*) (*b*)

Fig. 8. (*a*) Twenty-four-hour urinary sodium and calcium values during the control period and following the administration of 500 mg. Diamox orally on two consecutive days (indicated by arrows). (*b*) Mean seven day values of 24-hour urinary sodium and calcium during control and Diamox periods. A Diamox period consisted of the consecutive days on which 500 mg. Diamox was administered plus the five following days. The broken line represents a 12-day period, Diamox being administered on seven consecutive days.

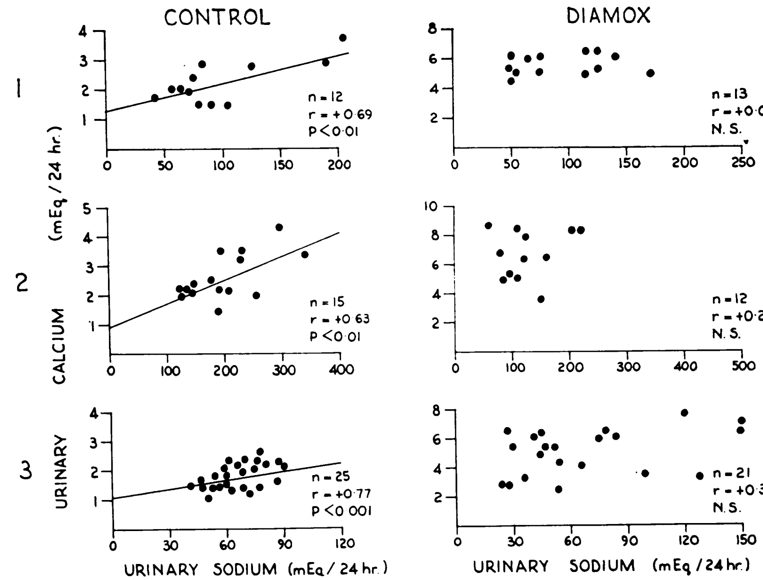


Fig. 9. Relation between 24-hour urinary sodium and calcium in three normal adult males during control and Diamox periods. A Diamox period consisted of the consecutive days on which 500 mg. Diamox was administered plus the five following days.

The effect of this alteration in the daily pattern of sodium and calcium excretion on the daily urinary sodium/calcium ratio is shown in Figure 10. The daily urinary sodium/calcium ratio fell during each Diamox period (a Diamox period consisting of the days on which Diamox was administered plus the five subsequent days). The difference in the mean daily urinary sodium/calcium ratio between the control period and the Diamox period

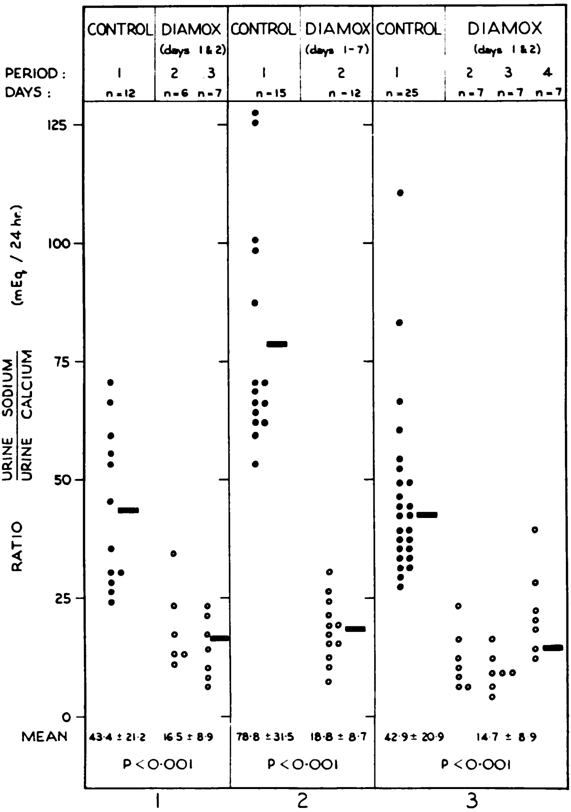


Fig. 10. Twenty-four-hour urinary sodium/calcium ratio in three normal adult males during control and Diamox periods. A Diamox period consisted of the consecutive days on which 500 mg. Diamox was administered plus the five following days. The horizontal bar indicates the mean value.

was highly significant in each instance ($P < 0.001$). The daily values of urinary sodium/calcium ratio during the Diamox periods and the 24-hour urinary sodium/calcium ratio in individual stone patients are shown in Figure 11. It is apparent that the range is similar. The mean daily urinary sodium/calcium ratio of the Diamox periods did not differ significantly from the mean 24-hour urinary sodium/calcium ratio of the stone cases. These findings provide strong support for the concept of an inverse relationship between the 24-hour urinary sodium/calcium ratio and the liability to renal stone formation.

Unlike urinary calcium, the urinary sodium can be directly related to the dietary intake. Except when sweat losses are significant, the measurement of the 24-hour urinary excretion of sodium is an accurate measurement of minimal sodium intake in normal people (Dahl, 1960; Modlin, 1965). Under physiological conditions, therefore, the daily urinary sodium/

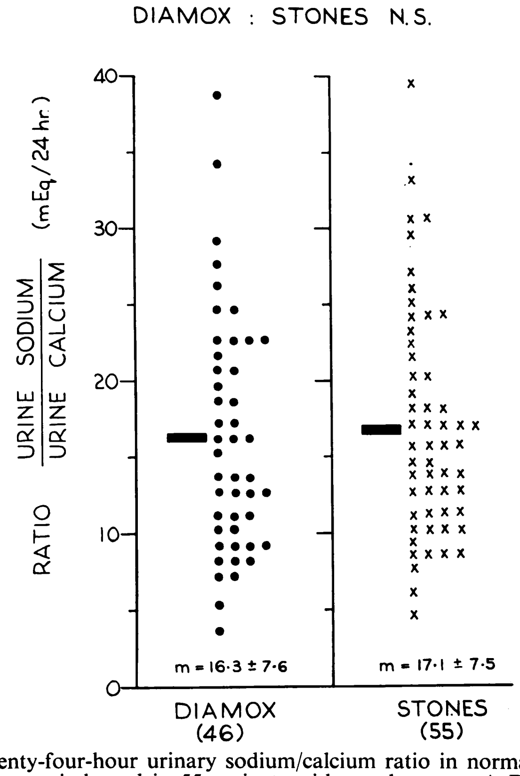


Fig. 11. Twenty-four-hour urinary sodium/calcium ratio in normal adult males during Diamox periods and in 55 patients with renal stone. A Diamox period consisted of the consecutive days on which 500 mg. Diamox was administered plus the five following days. The horizontal bar indicates the mean value.

calcium ratio would be influenced primarily by the dietary intake of sodium. The average 24-hour urinary sodium output, and presumably therefore the minimal daily intake in the Bantu, was 292 milliequivalents of sodium, or 17 gm. of sodium chloride, which is considerably higher than that usually quoted for Western communities, the several available estimates being in general agreement that average salt intakes in Western communities approximate 10 gm. per day (Dahl, 1959). Salt appetite is acquired rather than innate and a high salt intake appears to be a dietary peculiarity of the Bantu, the excess of salt being taken mainly as seasoning or table salt. The clinical and experimental evidence presented in this study suggests that it is this dietary custom of the Bantu that is responsible for their freedom from renal stones, the resulting high urinary sodium/calcium ratio appearing to constitute a physiological crystallization inhibitor mechanism. It seems likely that even if a crystal nucleus of hydroxy apatite is formed in the urine the concentration of sodium relative to calcium in solution would tend to prevent the further process of epitaxy and crystal aggregation by the competitive substitution of lattice ions, the calcium ions being displaced from the solid by the entering sodium ions.

Further evidence in support of this concept was sought.

Geographical " stone areas " have frequently been described in studies pertaining to the aetiology of renal stone and a dietary basis for this has been suggested from time to time. It is known that salt intakes may vary widely among different peoples and it seemed reasonable to enquire into average daily urinary levels of sodium and the incidence of renal stone in various population groups. A detailed investigation of this nature was beyond the scope of the present study, but the results of some preliminary enquiries are presented.

Salt intake in the Japanese has been extensively studied in relation to the incidence of cerebro-vascular disease in that country. Average levels of salt intake are high and are related to long-standing eating habits, the salt being taken mainly in soy sauce, miso and pickles. The salt intake appears to decrease from North to South, ranging from an average of 18.3 gm. per day in the Hokkaido region in the North to an average of 14 gm. per day in the Chugoku region in the South (Sasaki, 1964). The incidence of renal stone, assessed as a percentage of all urological patients seen at hospitals in the particular region, increases from North to South, being 1.8 per cent in the Hokkaido region and 8 per cent in the Chugoku region (Inada, 1966). There appears, therefore, to be an inverse relationship between the average levels of salt intake in a particular region and the incidence of renal stone. The incidence of renal stone in the Hokkaido region (1.8 per cent) is also much lower, for example, than the incidence of renal stone in Leeds, which has been similarly assessed at 8.6 per cent (Williams, 1963), where the population presumably has a salt intake approximating the average levels found in other Western communities and is probably close to the salt intake in the Chugoku region (the normal white subjects in this study had an average salt intake of 12.4 gm.). It is also interesting to observe that the incidence of renal stone has increased in Japan during the period 1955 to 1964 as compared with the period 1945 to 1954. Could this be related to alterations in dietary habits accompanying post-war Westernization?

It has previously been reported that the Eskimos have a low average daily intake of salt (Dahl, 1960). Enquiries were accordingly made concerning the incidence of renal stone in this population group, and the information obtained from personnel responsible for their medical care indicated that renal stones rarely occur among these people and, in fact, scrutiny of the records of one hospital dealing primarily with Eskimo patients had failed to reveal a proven case of renal stone. Arrangements were made for the analysis of 24-hour collections of urine obtained from Eskimos in various regions, and I am indebted to Dr. J. E. Logan of Ottawa for carrying out the various estimations. The data obtained in this manner confirmed that the Eskimos did in fact have a low average daily intake of salt. The mean 24-hour urinary sodium output, and presumably therefore the mean daily intake, was 81 milliequivalents of sodium or 4.8 gm. of sodium chloride. Their daily output of calcium was also surprisingly low, the mean 24-hour value being 50 mg., which is even lower than that found in the Bantu. The mean 24-hour urinary sodium/calcium ratio was 99.0, which does not differ significantly from the value of 104.8 found in the Bantu. This similarity between the mean urinary sodium/calcium ratio in two different population groups in which renal stone rarely occurs would seem to be more than a coincidence.

Several investigators have reported a marked family history of renal stone. Melick and Henneman (1958) found a family history in 12.5 per cent of their renal stone patients, and McGeown (1960) reported that the incidence of a family history of renal stone was 20 per cent. It is tempting to suggest that these observations could also best be explained on a dietary basis, such as group salt-eating habits.

It must be emphasized that these observations are of a very preliminary nature. The trends that are shown are most interesting, however, and tend to support the conclusions reached in the main part of this study.

ACKNOWLEDGEMENTS

I would particularly like to acknowledge my gratitude to Professor L. N. Pyrah, who first stimulated my interest in the subject of renal stones. I am indebted to Dr. W. P. U. Jackson for so generously allowing me to use his Endocrine Research Laboratory. I would also like to thank Professor J. F. Brock for granting me access to the facilities of his department, and Professor J. H. Louw for assisting in the establishment of the Renal Stone Clinic. This work was supported by grants from the South African Council for Scientific and Industrial Research and the Staff Research Fund of the University of Cape Town.

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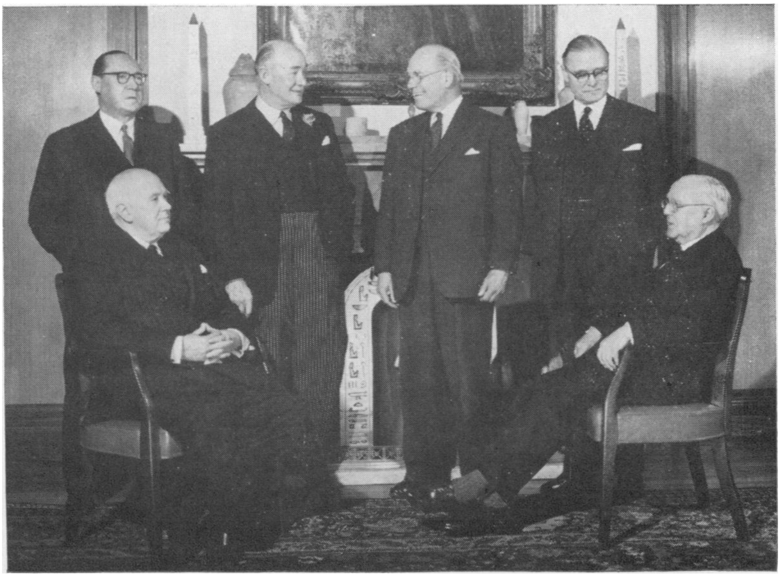
POST-WAR PRESIDENTS

IT RARELY HAPPENS in the Royal College of Surgeons of England that there are six successive Presidents all of whom are still active in the affairs of the College. This photograph was taken in the Bland-Sutton Room (Fellows' Common Room) of the College in January 1967 as a record of this fact.



Left to right: (*seated*) Sir Cecil Wakeley (1949–54), Sir Harry Platt (1954–57); (*standing*) Lord Brock (1963–66), Sir Arthur Porritt (1960–63), Sir James Paterson Ross (1957–60), Professor Hedley Atkins (1966–).

SURGERY LECTURES

THE SPRING COURSE of surgery lectures commences on Monday, 3rd April, and continues until Friday, 21st April. Full details of the lectures can be obtained from Mr. W. Webber at the Royal College of Surgeons of England. Attendance at the lectures is unrestricted. Fees for lectures are 10 gns. for the whole course or 10s. for a single lecture.